the composition having an energy density of about 1.5 kcal/ml and a ratio of non-protein calories per gram of nitrogen of at least about 90:1.

10. (Twice Amended) A method for providing nutrition to a metabolically stressed patient comprising the step of administering to the patient a therapeutically effective amount of a composition comprising:

a protein source comprising approximately 15% to about 18% of the energy of the composition;

a carbohydrate source; and

a lipid source including a mixture of medium and long chain triglycerides, the enteral composition having a caloric density of about 1.5 kcal/ml.

Please cancel claims 9 and 15 without prejudice or disclaimer.

REMARKS

In the Office Action, claims 1-15 are provisionally rejected under the judicially created doctrine of obviousness–type double patenting; and claims 1 and 3-15 are rejected under 35 U.S.C. §§ 102 and/or 103. Claims 1, 4 and 10 have been amended; and claims 9 and 15 have been cancelled. Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with Markings to Show Changes Made**." Applicants respectfully submit that the rejections have been overcome or are improper in view of the amendments and for the reasons set forth below.

In the Office Action, claims 1-15 are provisionally rejected under the judicially created doctrine of obviousness–type double patenting as being unpatentable over claims 1-22 of co-pending U.S. Patent Application No. 09/759,037. In response, Applicants respectfully submit that upon Notice of Allowability of either one of the co-pending applications that a Terminal Disclaimer will be filed to address this rejection. Applicants further note that this provisional rejection should be rendered moot with respect to claims 2, 9 and 15. In this regard, claim 2 was previously cancelled and claims 9 and 15 also have been cancelled as previously discussed. Therefore, Applicants believe that they have been fully responsive to this provisional rejection.

In the Office Action, claims 1, 3-7 and 9-15 are rejected under 35 U.S.C. § 102 as being anticipated by U.S. Patent No. 5,504,072 ("*Schmidl*"). The Patent Office essentially argues that *Schmidl* discloses or suggests under the principles of inherency each and every feature of the claimed invention as defined in claims 1, 3-7 and 9-15.

Applicants believe that this rejection is improper. Of the pending claims, claims 1, 4 and 10 are the sole independent claims. Independent claim 1 recites an enteral composition designed for metabolically stressed patients that includes a protein source with about 15% to about 18% of the energy of the composition; a carbohydrate source; and a lipid source including a mixture of medium and long chain triglycerides wherein the enteral composition has a caloric density of about 1.5 kcal/ml. Independent claim 4 recites an enteral composition for a metabolically stressed patient that includes about 15% to about 18% of the energy of the composition of partially hydrolysed whey protein; a carbohydrate source; and a lipid source including a mixture of medium and long chain triglycerides wherein the composition has an energy density of about 1.5 kcal/ml and a ratio on non-protein calories per gram of nitrogen of at least about 90:1. Independent claim 10 recites a method of providing nutrition to a metabolically stressed patient that includes administering to the patient a therapeutically effective amount of a composition. The composition includes a protein source including approximately 15% to about 18% of the energy composition; a carbohydrate source; and a lipid source including a mixture of medium and long chain tryglycerides wherein the enteral composition has a caloric density of about 1.5 kcal/ml.

The claimed invention provides a product that is specifically directed to meet nutritional needs of metabolically stressed patients without elevated protein levels or excess fluid. To this end, the claimed invention provides calorically dense nutritional support in the form of an enteral composition while at the same time providing a moderate non-protein calories per gram of nitrogen ("NPC/gN") ratio. As previously discussed, the enteral composition of the claimed invention includes, in part, a protein source that provides about 15% to about 18% of the total energy of the composition wherein the enteral composition has a caloric density of at least about 1.4 kcal/ml. For adults and older children (10 plus years or older), for example, the protein concentration is optimal for the moderate tissue repair needs of the targeted patient populations without imposing an undue nitrogen burden on renal function. See, specification, Page 4, lines 4-17.

In contrast, *Schmidl* clearly fails to disclose or suggest a number of features of the claimed invention. Of course, an anticipation rejection requires that "there must be no difference between the claimed invention and a reference's disclosure as viewed by a person of ordinary skill in the filed of the invention." *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565 (Fed. Cir. 1991). Accordingly, "for a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference." *In re Bond*, 910 F.2d 831 (Fed. Cir. 1990).

For example, *Schmidl* fails to disclose or suggest, an enteral composition that has a caloric density of about 1.5 kcal/ml as required by the claimed invention. As previously discussed, the enteral composition of the claimed invention provides nutritional support in the form of increased energy density without elevated protein levels or excess fluid. This is important to meet the needs of metabolic stressed patients, that is, the patient population as defined in Applicants' claimed invention. Indeed, *Schmidl* states "the composition can also be in the form of a ready-to-use aqueous liquid which preferably has a caloric content of 1 kcal/ml." See, *Schmidl* column 7, lines 54-57. If anything, this clearly teaches away from the claimed invention.

Further, Applicants believe that it is clearly improper to justify the anticipation rejection based on principles of inherency as the Patent Office appears to have done. Of course, the Court of Appeals for the Federal Circuit has held that "[a]n inherent limitation is one that is necessarily present; invalidation based on inherency is not established by probabilities or possibilities." *Scaltech, Inc. v. Retec/Tetra, LLC.*, 51 USPQ 2d 1055, 1059 (Fed. Cir. 1999). The mere fact that a composition has lipids, carbohydrates, and protein does not mean the composition has the same caloric density as another composition including lipids, carbohydrates, and proteins. Simply because a product has lipids, carbohydrates, and protein does not mean it has the same characteristics as another product having lipids, carbohydrates, and protein. There are millions of compositions including a lipid, a carbohydrate, and a protein that have different properties. Thus, clearly the Patent Office's inherency position is improper for at least this reason. Therefore, Applicants believe that *Schmidl* fails to anticipate the claimed invention as defined in claims 1, 3-7 and 9-15. Moreover, this rejection should be rendered moot with respect to claims 9 and 15 as these claims have been cancelled as previously discussed.

Accordingly, Applicants respectfully request that the anticipation rejection be withdrawn.

In the Office Action, claims 1 and 10-15 are rejected under 35 U.S.C. § 102 as being anticipated by U.S. Patent No. 5,221,668 ("*Henningfield*"). Applicants believe that *Henningfield*, like *Schmidl*, fails to disclose or suggest a number of features of the claimed invention.

For example, Applicants do not believe that *Henningfield* discloses or suggests an enteral composition for metabolically stressed patients that includes, in part, a protein source, such as partially hydrolysed whey proteins, that include about 15% to about 18% of the energy of the composition. As previously discussed, Applicants have found that the total amount of energy from about 15% to about 18% provided by the protein source is optimal for moderate tissue repair needs of the targeted patient populations without imposing an undue nitrogen burden on renal function.

Indeed, *Henningfield* discloses that about 20.5% of the calories provided by proteins is preferred. Further, the *Henningfield* composition is intended for trauma patients, especially severe injury. See, *Henningfield*, column 1, lines 1-15. As previously discussed, the enteral compositions of the claimed invention are designed for metabolically stressed patients, particularly patients that have compromised absorptive capacity. For at least those noted reasons, Applicants believe that one skilled in the art viewing would clearly consider *Henningfield* to be deficient with respect to a number of features of the claimed invention. Therefore, Applicants believe that *Henningfield* fails to anticipate the claimed invention.

Accordingly, Applicants respectfully request that this rejection be withdrawn.

In the Office Action, claims 1 and 3-15 are rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Patent No. 5,714,472 ("*Gray*") in view of *Schmidl*. The Patent Office primarily relies on *Gray* and, thus, attempts to remedy the deficiencies with *Gray* with the remaining cited art.

At the outset, claims 9 and 15 have been cancelled as previously discussed. Thus, the obviousness rejection with respect to same should be rendered moot and therefore withdrawn as a matter of law.

With respect to the remaining pending claims at issue, claims 1, 4 and 10 are the sole independent claims. Claims 1 and 4 relate to an enteral composition designed for metabolically stressed patients; and claim 10 relates to a method for providing nutrition to a metabolically stressed patient as previously discussed. In general, the enteral composition of the claimed

invention includes a protein source, a carbohydrate source and a lipid source. The protein source, such as a partially hydrolysed whey protein, provides from about 15% to about 18% of the energy of the composition. The enteral composition of the claimed invention has a caloric density of about 1.5 kcal/ml. As previously discussed, the enteral compositions of the claimed invention provide nutritional support in the form of increased energy density without elevated protein levels or excess fluid to meet the needs of metabolically stressed patients.

Applicants are submitting herewith additional scientific evidence that demonstrates the desirable characteristics of the present invention. In this regard, the scientific evidence is provided in the form of scientific publications attached hereto as Exhibits A-F. In general, the scientific evidence is based on a comparison of two types of nutritional formulas, namely, PEPTAMEN 1.0® and PEPTAMEN 1.5® which are administered to patients who are in a state of metabolic stress in urgent need of increased energy according to an embodiment of the present invention. As detailed below, the scientific evidence demonstrates that patients prefer the high energy formula made in accordance to an embodiment of the present invention because feeding time and feeding amount was reduced, thus allowing for other activities to take place, such as going to school.

For example, Exhibit A provides a study conducted on a 14-year old female with an 8-year history of Crohn's disease. After transition from 1.0 to 1.5 cal/cc formula, feeding time was reduced by more than 50%; the subject could go to school; and the subject experienced a 32% weight gain. See, *J. M. Murdy et al.*, HIGH CALORIE ELEMENTAL DIET IMPROVES OUTCOMES AND QUALITY OF LIFE FOR TUBE FED ADOLESCENTS, Abstract (1999).

As disclosed in Exhibit B, a woman of 21 years and pregnant for 28 weeks (RK) suffered a malrotation of the small intestine. After months of hospitalization, she received a quadruple organ transplant of the small bowel, liver, kidney and pancreas. RK immediately started feeding with a powdered amino-acid based, liquid formula which was poorly tolerated. The formula was changed to a formula according to an embodiment of the present invention which was immediately tolerated. Within a year, RK's weight returned from 117 to 130 lbs. See, Exhibit B, *R. S. Kindle et al.*, HIGH CALORIE PEPTIDE-BASED, LIQUID, ELEMENTAL, ENTERAL FORMULA IS WELL-TOLERATED BY PATIENT WITH QUADRUPLE ORGAN TRANSPLANT, Abstract (2002).

As disclosed in Exhibit C, a 42-year old male with chronic pancreatitis, irritable bowel and a history of alcohol abuse was maintained on total parentral nutrition for 14 weeks. Despite increasing energy intake, he lost weight.

The diet was then changed to a 1.0 kcal/ml and later to the 1.5 kcal/ml whey-based peptide diet according to an embodiment of the present invention. The formula change and increased energy intakes were well tolerated. Liver enzymes returned to normal within four weeks of the enteral therapy and the patient gained weight. See, Exhibit C, *J. Meyer*, HOME ENTERAL NUTRITION IN CHRONIC PANCREATITIS: A CASE REPORT, Support Line, pp. 7-10 (2000). *J. Meyer et al.*, ENTERAL NUTRITION IN CHRONIC PANCREATITIS: COST SAVINGS WITH THE USE OF A 1.5 KCAL/ML PEPTIDE-BASED DIET, Abstract (1999).

As disclosed in Exhibit D, children suffering from Crohn's disease were normally given a 1 kcal/ml standard defined formula that had to be consumed in a large volume. A retrospective analysis was performed to evaluate the effect of the use of condensed semi-elemental diet (a 1.5 kcal/ml diet made in accordance with an embodiment of the present invention) on the acceptability, tolerance, weight gain and efficacy of nutritional therapy for pediatric CD patient. Patients preferred the reduced volume of condensed product required to meet their nutritional needs. See, Exhibit D, *L. Bouthiller et al.*, USE OF CONDENSED SEMI-ELEMENTAL DIET IN THE TREATMENT OF PEDIATRIC CROHN'S DISEASE, p. 74 (2002).

As disclosed in Exhibit E, gastric emptying rate of equal volumes of two whey-based formulas of different energy density and osmolality was studied in ten children ranging in age from 4½ to 12 years. Gastric emptying rates of the two formulas were comparable. Over a one-month clinical trial, substitution of the lower energy density whey-based formula with an equal volume of the high density formula produced a mean-weight gain of 1.17 kg per patient without change in tolerance. See, Exhibit E, *V. Khoshoo*, GASTRIC EMPTYING OF TWO WHEY-BASED FORMULAS OF DIFFERENT ENERGY DENSITY AND ITS CLINICAL IMPLICATION IN CHILDREN WITH VOLUME INTOLERANCE, European J. of Clinical Nutrition, v. 56, pp. 1-3 (2002).

As disclosed in Exhibit F, children suffering from cystic fibrosis (CF) were given the formula according to an embodiment of the present invention. All four children experienced weight gain. See, *J. A. Fulton, et al.* USE OF A READY-TO-FEED, SEMI-ELEMENTAL

FORMULA FOR GASTRONOMY TUBE FEEDINGS IN CHILDREN WITH CYSTIC FIBROSIS, Abstract 77 (1999).

In contrast, Applicants believe that the cited art, even if combinable, fails to disclose or suggestion a number of features of the claimed invention. For example, the *Gray* references fails to disclose or suggest an enteral composition that is specifically designed to meet the needs of metabolically stressed patients as required by the claimed invention. In part, the claimed enteral compositions include a protein source, such as partially hydrolysed whey proteins, with 15% to about 18% of the energy content of the composition. Indeed, the Patent Office even admits that *Gray* merely provides "about 22%" of the energy of the composition. See, Office Action dated March 27, 2002, page 7.

Contrary to the Patent Office's position, this clearly is not substantially the same nor does it suggest an enteral composition with a protein energy content of about 15% to about 18% as required by the claimed invention. Further, *Gray* merely discloses that the total non-protein calories per gram of nitrogen should be less than or equal to 70:1. This clearly contrasts claim 4 which requires, in part, a ratio of non-protein calories per gram of nitrogen of at least about 90:1. Moreover, Applicants have provided scientific evidence that clearly demonstrates the beneficial effects of the specific nutritional properties of the present invention as previously discussed. Therefore, *Gray* is clearly deficient with respect to the claimed invention.

Applicants further submit that the Patent Office cannot rely solely on *Schmidl* to remedy the deficiencies of *Gray*. As previously discussed, *Schmidl* is clearly deficient as well with respect to the claimed invention, particularly with respect to the energy density content of the enteral composition as required by the claimed invention. Thus, Applicants do not believe that one skilled in the art would be inclined to modify *Gray*, let alone be motivated to combine *Gray* and *Schmidl* in the first place, to arrive at the claimed invention. What the Patent Office clearly has done is to simply piece together the cited art by selectively picking and choosing teachings from disparate art in an attempt to explain what the claimed invention discloses. The Court of Appeal for the Federal Circuit has criticized this motivation to combine analysis as being "hindsight reconstructive" because the motivation to combine the references was first disclosed in the present invention. *In re O'Farrell,* 853 F.2d 894, 902-903 (Fed. Cir. 1988). Indeed, both *Schmidl* and *Gray* effectively teach away from an enteral composition that includes both a protein source with about 15% to about 18% of the energy of the composition and wherein the

composition has a caloric density of about 1.5 kcal/ml. Again, the claimed enteral compositions have been specifically designed to meet the needs of metabolically stress patients. As previously discussed, Applicants have provided scientific evidence that demonstrate the beneficial effects of the specific nutritional characteristics of the present invention. Therefore, Applicants believe that *Gray* and *Schmidl,* even if combinable, fail to render obvious the claimed invention.

Accordingly, Applicants respectfully request that this rejection be withdrawn.

For the foregoing reasons, Applicants respectfully request reconsideration of the present application and earnestly solicit allowance of same.

Respectfully submitted,

BELL, BOYD & LLOYD LLC

BY _____

Robert M. Barrett
Reg. No. 30,142
P.O. Box 1135
Chicago, Illinois 60690-1135
Phone: (312) 807-4204

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 1, 4 and 10 have been amended as follows:

1. (Twice Amended) An enteral composition designed for metabolically stressed patients comprising:

a protein source providing about 15% to about 18% of the energy of the composition;

a carbohydrate source; and

a lipid source including a mixture of medium and long chair triglycerides, the enteral composition having a caloric density of ~~at least~~ about 1.45 kcal/ml.

4. (Twice Amended) An enteral composition for a metabolically stressed patient comprising about 15% to about 18% of the energy of the composition of partially hydrolysed whey protein;

a carbohydrate source; and

a lipid source including a mixture of medium and long chain triglycerides;

the composition having an energy density of ~~at least~~ about 1.45 kcal/ml and a ratio of non-protein calories per gram of nitrogen of at least about 90:1.

10. (Twice Amended) A method for providing nutrition to a metabolically stressed patient comprising the step of administering to the patient a therapeutically effective amount of a composition comprising:

a protein source comprising approximately 15% to about 18% of the energy of the composition;

a carbohydrate source; and

a lipid source including a mixture of medium and long chain triglycerides, the enteral composition having a caloric density of ~~at least~~ about 1.45 kcal/ml.

Claims 9 and 15 have been cancelled without prejudice or disclaimer.

EXHIBIT A

ADA '99

TITLE:
HIGH CALORIE ELEMENTAL DIET IMPROVES OUTCOMES AND QUALITY OF LIFE FOR TUBE FED ADOLESCENTS

AUTHOR(S):
J.M. McMurdy, RD, CNSD, Optima Health Home Medical Equipment, Manchester, NH

LEARNING OUTCOME:
To identify a key factor in formula selection for adolescents.

ABSTRACT TEXT:
Adolescence presents unique nutritional challenges due to the physical and psychosocial changes which define it. These challenges can be magnified by the need for nutrition support. The use of a 1.5 calorie per cc product in two adolescent home enteral patients requiring an elemental diet resulted in improvements in both physical and psychosocial parameters.

Case 1: A 14 year old female with an 8 year history of Crohn's disease was managed at home for two years with 500 cc of a 1.0 cal/cc elemental diet nocturnally. A disease exacerbation resulted in loss of 15% body weight (12 lbs) and the need for continuous feedings, which precluded her return to school. Transitioning to a 1.5 cal/cc formula reduced feeding time by >50% (to 11 hours) and allowed her to return to school. Over 6 months time she experienced a 32% weight gain (22 lbs).

Case 2: A 13 year old female with cystic fibrosis and failure to thrive (weight for age <5th%ile) was started on 500 cc of a 1.0 cal/cc elemental diet in preparation for double lung transplant. As her volume needs increased monthly due to inadequate weight gain, it became more difficult to schedule feeding time due to after-school activities and the frequent absence of an adult at home. Switching to the 1.5 cal/cc formula enabled her to increase her rate of weight gain by 70%, from an average 4.5 g/day over 5 months to 7.7 g/day over 2 months. She thus achieved the 25th%ile goal weight needed for surgery, while maintaining her level of social activity.

The 1.5 cal/cc elemental diet supported the extraordinary demands of illness and adolescent growth while affording both patients greater independence and normalcy. The familiar benefits of a calorically dense enteral formula have been successfully demonstrated in adolescents requiring an elemental diet.

EXHIBIT B

N16

HIGH CALORIE, PEPTIDE-BASED, LIQUID, ELEMENTAL, ENTERAL FORMULA IS WELL-TOLERATED BY PATIENT WITH QUADRUPLE ORGAN TRANSPLANT

R. S. Kindle, Baylor University Medical Center Grapevine, TX, Bedford, TX; T. E. Ritter, Baylor University Medical Center Grapevine, TX, Grapevine, TX

In Jan 1991, RK was 21 years old and 28 weeks pregnant when she suffered a malrotation of the small intestine. Within 12 hours of the infarction, she underwent emergency surgery to remove her gangrenous intestinal tract, leaving only her stomach, duodenum, and descending colon. She left the hospital on nocturnal TPN; her weight was 117 lbs. (IBW/UBW = 130 lbs.). For the next three years, RK remained on TPN; her weight increased to 130 lbs. In 1995 her liver enzymes and bilirubin began to rise, but she remained asymptomatic. In late 1999, she became extremely jaundiced was soon in liver failure. RK was evaluated for a liver and small bowel transplant and while awaiting a donor, she developed severe HTN, internal bleeding/coagulation disorder, renal failure, pneumosistis pneumonia, and other complications. After months of hospitalization, she received a quadruple organ transplant: Small bowel, liver, kidney, and pancreas. Her remaining stomach and duodenum were removed and the donor small intestine was attached proximately to her esophagus and distally to her descending colon. RK was immediately started on an NG feeding with a powdered amino-acid-based elemental formula, which was poorly tolerated. The formula was changed to a high-calorie, peptide-based, liquid, low-osmolality elemental formula, which was immediately tolerated. RK went home on this peptide-based elemental formula providing 1875 kcal and 75 g protein/day. She also ate low-residue foods as tolerated. Within a year, RK's weight returned to 130 lbs and she decided to discontinue the NG feedings and rely only on oral intake. RK's weight fell to 103 lbs., diarrhea was continuous, and it was necessary to reinitiate TPN. Her oral intake continues as tolerated, but diarrhea and malabsorption persist. NG feedings are not an option due to nasal ulcers and scarring; NJ feedings are contraindicated. RK is considering returning to an oral version of the high-calorie, peptide-based, liquid, low-osmolality elemental formula, as it was the only enteral nutrition that was absorbed and tolerated by her fragile GI tract.

Nutrition Week
2002

NEOSAN PHARMACEUTICALS

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EXHIBIT C

Hom Ent ral Nutrition in Chronic Pancreatitis: A Cas Report

Julie Meyer, RD, CNSD

Abstract

A growing body of research supports the use of jejunal enteral feedings for patients with chronic or mild pancreatitis. This case study demonstrates that administration of a high-calorie, peptide-based diet can improve clinical outcomes and results in significant cost savings for a home-care patient with chronic pancreatitis when compared with parenteral nutrition (1).

Introduction

Chronic pancreatitis is characterized by irreversible damage to the pancreas, as evidenced by tissue calcification. The most common symptoms include recurrent abdominal pain, weight loss, and steatorrhea, which can often lead to progressive malnutrition (2–5). Excessive and prolonged alcohol consumption accounts for 60% to 75% of cases of chronic pancreatitis, and in many cases, the disease continues to progress even after abstinence (2–5). Cigarette smoking has also been suggested as a contributing factor (3). Other etiologies include congenital predisposition, neoplasia, trauma, and m tabolic diseases such as hyperlipidemia, cystic fibrosis, or hyperparathyroidism (2,3,6). The gallstones and dyskinesia that can cause acute pancreatitis are not associated with the chronic form of the disease. (2,3). Nutrition support is frequently required during severe exacerbations of chronic pancreatitis.

Parenteral nutrition has been the traditional mode of nutrition support for patients with pancreatitis. Recent literature, however, suggests that enteral nutrition can be safe and cost-effective. Enteral feeding is the preferred route of nutrition support, depending on the severity of disease and patient tolerance (2,4,7), because there is less risk of the metabolic abnormalities, intestinal atrophy, sepsis, and infection that have been associated with total parenteral nutrition (TPN). No significant increase in pancreatic excretion has been documented with jejunal infusion of nutrients. Therefore, jejunal administration of nutrients should not aggravate pancreatic inflammation, allowing the pancreas to "rest" (2,4,6–12). Elemental formulas stimulate the pancreas and gastrointestinal tract less than standard intact protein formulas (2,8,9,11,12), and better absorption has been reported when using small peptide, semi-elemental formulas compared with free amino acid elemental formulas (2). The enteral formula that was initially used in this case study has been studied by Freedman (10,11) for use in patients with chronic pancreatitis and found to have a minimal effect on cholecystokinin (CCK) release. CCK, a hormone that is secreted into the blood via the small intestine, causes activation of pancreatic enzyme secretion during digestion of protein and fats. Minimal CCK release is important to allow the pancreas to "rest" (2,10,11).

The following case report illustrates the clinical, quality-of-life, and cost advantages of enteral nutrition compared with TPN in a home-care patient who had chronic pancreatitis.

Case Presentation

L.B., a 62-year-old white male, was hospitalized with severe abdominal pain and cachexia due to chronic calcific, alcohol-related pancreatitis. A Hickman catheter was placed and TPN initiated during hospitalization to rest the pancreas, provide pain relief, and treat his malnutrition. He was discharged to home after 2 days in the hospital on TPN of 150 mL/hr over 12 hours (1,790 mL of TPN plus lipids) and a clear liquid diet. Shortly after discharge, he was admitted to the home nutrition support service.

His past medical history included: alcoholic pancreatitis (cessation of drinking 20 years ago), alcoholic liver disease, gallbladder disease, chronic obstructive pulmonary disease with asbestos-related exposure, smoking (1 pack of cigarettes per day), irritabl bowel disease, diverticulosis, and chronic constipation. An earlier 14-month course of therapy included two endoscopic retrograde cholangiopancreatographies, biliary tree stent placement, forced dilatation of the extrinsic compression on the common bile duct, and two pancreatic sphincterotomies on separate occasions. Because he continued to complain of abdominal pain, a cholecystectomy and choledochoduodenostomy were performed. Finally, lithotripsy of the pancreas and flush-out of the major pancreatic ductal system via a nasal pancreatic tube with stone debridement were undertaken. However, none of these procedures provided long-term pain relief, and the patient subsequently received two separate celiac blocks. The goal of a celiac block is to block the pain response of afferent fibers that pass through the celiac plexus, which includes the pancreas and abdomen. A Whipple procedure (pancreatoduodenectomy) was not an option because of the inability to free the pancreas from major vessels in the area.

L.B. initially presented to the nutrition support service with malnutrition due to inadequate intake of food because of pain associated with eating and increased calorie needs due to catabolism. His anthropometric data and the details of nutrition therapy over the course of treatment are summarized in Table 1. He presented at 79% of usual body weight. Blood chemistries were monitored weekly while he received home parenteral nutrition (HPN), then bimonthly or monthly while receiving h me tube feedings. Most of the laboratory results (Table 2) remained relatively stable during the course of HPN, with

(Continued on next page)

the exception of liver function tests, including serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), and alkaline phosphatase. These values rose significantly during the fourth week of HPN therapy, began to plateau at week 7, and returned to normal once HPN was discontinued. These values were monitored to avoid the hepatic complications that may occur with long-term HPN. When the tube feeding started at week 14 of nutrition therapy, the SGOT and SGPT were in the normal range, but the alkaline phosphatase remained elevated at 308 U/L. It decreased to 130 U/L within 3 weeks of discontinuing the HPN. The decrease in hemoglobin, hematocrit, and iron concentrations over time most likely were due to chronic disease and low iron intake during HPN.

The initial HPN formula provided 30 kcal/kg (1.2 times the Harris-Benedict equation) and 1.8 g/kg protein. (Indirect calorimetry was not available.) Additionally, L.B. continued to drink clear liquids. Nevertheless, he experienced severe abdominal pain when drinking clear liquids, so the diet was discontinued during the third week of HPN. Despite HPN, his weight decreased to 46.4 kg (78% of usual body weight) by the fourth week of therapy. Calories were increased to 37 kcal/kg, and protein was maintained at 1.8 g/kg because albumin levels were normal. During the seventh week of HPN, L.B.'s weight had dropped to 45 kg (76% of usual body weight); energy support was increased to 42 kcal/kg and protein to 2.0 g/kg. Protein was increased to increase calories without additional carbohydrate because the patient was approaching the maximum oxidation rate of carbohydrate at 7 g/kg/day. Because L.B. no longer was reporting pain, another trial of a clear liquid diet was initiated at the seventh week of HPN. However, he again experienced abdominal pain and was made NPO.

Using pancreatic enzymes to decrease exocrine secretion from the pancreas can often relieve the abdominal pain associated with chronic pancreatitis when oral intake is initiated. It is believed that high doses of exogenous pancreatic enzymes "rest" the pancreas by minimizing CCK release (3). Patient compliance with enzyme therapy is essential for optimal pain control. L.B. admitted later that he was often noncompliant with the prescribed enzym therapy when he was eating because taking the prescribed amount of enzymes made him feel "bloated and full." He often complained of flatulence, abdominal cramping, and an orange greasy substance in his bowel movements. The most severe episodes of pain were associated with cramping before a bowel movement and pain with eating while on HPN. This condition was further complicated by his history of irritable bowel syndrome and chronic constipation.

Calories were increased again during the 11th week of HPN to 44 kcal/kg (120% of Harris-Benedict equation × 1.5) to promote weight gain because he continued to remain below goal weight. Hypermetabolism, with energy needs as high as 139% of basal energy expenditure, is most common with acute pancreatitis (61% of patients), but can also occur with chronic pancreatitis (33% of patients) (14,15). The greatest energy needs occur when pancreatitis is complicated by sepsis (14,15). Hebuterne and colleagues (14) found that more than 60% of nonseptic, undernourished patients who had alcohol-related chronic pancreatitis

Table 1. Selected Nutrition Support Data for L.B.

Week	1	4	7	11	14	18	50
Height	67 in (167.5 cm)						
Weight	46.8 kg	46.4 kg	45 kg	46 kg	46.8 kg	47.3 kg	51.4 kg
% Ideal Body Weight	77%	77%	74%	76%	77%	78%	85%
% Usual Body Weight	79%	78%	76%	76%	79%	80%	87%
Protein Provided by Nutrition Support (g/kg)	1.8	1.8	2.0	2.0	2.0	1.9	1.8
Energy Provided by Nutrition Support (kcal/kg)	30	37	42	44	43	47	44
Nutrition Support Diet	• TPN • CL	• TPN	• TPN • CL	• TPN • CL	• TF initiated • TPN continued • CL	• TF • Low-fat diet • TPN discontinued	• Regular diet • TF discontinued

TPN= total parenteral nutrition, CL= clear liquids, TF= tube feeding

were hypermetabolic. Nicotine has also been shown to increase metabolic rate (14).

During week 11, clear liquids were attempted again, with L.B. tolerating small amounts of juice, broth, sports drink, and gelatin, but experiencing episodes of both diarrhea and constipation with oral intake. Due to his continued weight loss, increased values on liver function tests, and maximal provision of calories and carbohydrate (7g/kg/d carbohydrate) in his HPN, the nutrition support service recommended a trial of jejunal tube feedings using a peptide-based formula. (The nutrition support service included a clinical medical advisor-physician, registered pharmacist, home infusion nurse, and certified nutrition support dietitian.) The change in feeding modality was discussed with L.B., who agreed. During the 14th week of HPN, a nasojejunal (NJ) tube was placed and a peptide-based formula (1.0 kcal/mL) initiated at 20 mL/hr for 10 hours during the day and gradually increased to a goal rate of 150 mL/hr with HPN infusion at night. No pancreatic enzymes were administered with tube feeding (unless he also was eating orally) because tube feeding in the jejunum would prompt minimal pancreatic secretion. HPN was tapered as the tube feeding increased to keep the nutrient intake consistent (approximately 2,000 kcal with 90 g protein per day). Because L.B. continued to work whil receiving nutrition therapy, a portable pump was used for daytime tube feeding infusion. During the 16th week of nutrition therapy, L.B. was gradually transitioned to a nutritionally equivalent 1.5 kcal/mL peptide-based formula infused at 150 mL/hr for 10 hours at night (2,250 kcal) to reduce the number of hours of tube feeding, and the HPN was discontinued. During the 17th week of therapy, L.B. was hospitalized with a Hickman catheter infection that necessitated catheter removal. His NJ tube had also migrated out of the jejunum and was repositioned with radiographic verification of placement.

During the transition to enteral feedings, L.B. experienced frequent abdominal discomfort (bloating, flatulence, and reflux), occasional heartburn, and abdominal cramping. He was advised to decrease the rate of tube feeding from 150 mL/hr to 125 mL/hr, but was reluctant to do this because he wanted to avoid additional hours of infusion. Some of these symptoms were attributed to the NJ tube migrating into the stomach. He continued to have weekly bouts of increased abdominal discomfort, gas, and an orange greasy substance in his bowel movements, which was attributed to fat malabsorption ass ciated with pancreatitis. L.B.'s occasional noncompliance with taking the prescribed amount of pancreatic enzymes during oral intake probably also contributed to the steatorrhea. The tube feeding formula had a high percentage of medium-chain triglyceride oil as its fat source to promote better absorption. Following the development of a sinus infection from the NJ tube, a percutaneous endoscopic jejunostomy feeding tube was placed during the 18th week of nutrition therapy.

L.B.'s diet was slowly advanced, and by the 30th week of nutrition therapy, he was tolerating small bland meals. Pancreatic enzymes were prescribed with all meals and snacks. He had not taken pancreatic enzymes during the tube feeding. His weight remained stable at 47.7 to 49.5 kg for 6 months while receiving the tube feeding at the goal feeding rate.

During week 48, L.B. developed a left spontaneous pneumothorax, causing significant respiratory failure, and was hospitalized for drainage of the pneumothorax. He quit smoking at this time and reported reduced shortness

(Continued on next page)

Table 2. Selected Laboratory Values for L.B.

Week				11	14	18	
Albumin (g/dL) (normal 3.0 to 5.1 g/dL)				3.4	3.0		
SGPT (U/L) (normal 0 to 55 U/L)				89	34		
SGOT (U/L) (normal 5 to 35 U/L)			47	47	39		
Alkaline phosphatase (U/L) (normal 31 to 115 U/L)				394	308	130	
Hemoglobin (g/dL) (normal 12 to 16 g/dL)				10.7	10.9	11.8	
Hematocrit (%/dL) (normal 35 to 46 %/dL)				32.5	33.8	36.1	

Bolded figures in table signify values out of normal range.

of breath and cough and improved appetite. On week 50 of nutrition therapy (approximately 7 months after start of the tube feeding), L.B.'s weight was up to 51.4 kg, he was tolerating a low-fat diet, and the tube feeding was discontinued. His weight continued to increase over the next year, he returned to his usual body weight of 57.6 to 58.5 kg, and he has not experienced any recurrence of pancreatitis for 2 years.

Conclusion

The benefits of enteral nutrition compared with parenteral nutrition in this patient with chronic pancreatitis were evidenced by improved clinical outcomes, including normalization of liver function tests, energy level, and weight gain. Significant cost savings from enteral therapy were calculated as $625 per week, $2,500 per month, and $30,000 per year. L.B. did not always comply with his low-fat, high-fiber diet or with his pancreatic enzyme therapy. However, we were fortunate to work with a patient who was willing to have an NJ tube initially for enteral feeding and continue the administration of jejunal feeding for th necessary length of time.

Julie Meyer, RD, CNSD, is a clinical dietitian at HealthPartners, Bloomington, Minn.

Julie's mentor was Janet Furman Simmons, MS, RD, who is a nutrition support clinician at Rush-Presbyterian-St. Luke's Medical Center, Chicago, Ill.

References

1. Meyer J, Smith J. Enteral nutrition in chronic pancreatitis. *J Am Diet Assoc.* 1999;99 (suppl):A–105. Abstract.
2. McClave S, Snider H, Sexton L, Owens N. Nutrition in pancreatitis. In: *The A.S.P.E.N. Nutrition Support Practice Manual.* Silver Spring, Md: American Society of Parenteral and Enteral Nutrition; 1998:13-1–13-10.
3. Holt S. Chronic pancreatitis. *South Med J.* 1993;86:201–207.
4. Steer M, Waxman I, Freedman S. Chronic pancreatitis. *N Engl J Med.* 1995;332:1482–1490.
5. Holthouse B. Pancreatitis: a comprehensive review. *Support Line.* 2000;22(1):3–10.
6. Stralovich A. Gastrointestinal and pancreatic disease. In: Gottschlich MM, Matarese LE, Shronts EP, eds. *Nutrition Support Dietetics Core Curriculum.* 2nd ed. Silver Spring, Md: American Society of Parenteral and Enteral Nutrition; 1993:275–310.
7. McClave S, Greene L, Snider H, Makk L, Cheadle W, Owens N, Dukes L, Goldsmith L. Comparison of the safety of early enteral vs. parenteral nutrition in mild acute pancreatitis. *JPEN.* 1997;21:14–20.
8. Grant J, Davey-McCrae J, Snyder P. Effect of enteral nutrition on human pancreatic secretions. *JPEN.* 1987; 11:302–304.
9. Ragins H, Levinson S, Singer R, Stamford W, Seifter E. Intrajejunal administration of an elemental diet at neutral pH avoids pancreatic stimulation. *Am J Surg.* 1973;126:606–614.
10. Freedman S. Role of enteral nutrition in the treatment of chronic pancreatitis. *Proceedings of the American Society of Parenteral and Enteral Nutrition Clinical Congress 1999.* Silver Spring, Md: American Society of Parenteral and Enteral Nutrition; 1999:407–410.
11. Freedman S. Peptamen: a novel therapy in patients with chronic pancreatitis. *Gastroenterology.* 1997;112:A267. Abstract.
12. Woodward J, Colagiovanni L. Feed the patient, fool the pancreas. *Nursing Times.* 1998;94(8):65–67.
13. Bock, M. Effects of pancreatitis on nutritional status and nutrient intake: a case study. *Support Line.* 2000; 22(1):11–17.
14. Hebuterne X, Hastier P, Peroux J, Zeboudj N, Delmont J, Rampal P. Resting energy expenditure in patients with alcoholic chronic pancreatitis. *Dig Dis Sci.* 1996;41:533–539.
15. Dickerson R, Vehe K, Mullen J, Feurer I. Resting energy expenditure in patients with pancreatitis. *Crit Care Med.* 1991;19:484–490.

November 1, 2000

Dear Nutrition Support Dietitian:

Many of you entrust your home nutrition support patient's needs to Coram Healthcare. We appreciate your trust and share your interest in dependable, high-quality service.

For 20 years, Coram's history has been built upon quality care, clinical excellence, and customer service. We have contributed to the health and healing of millions across the country, earning a reputation for superior care, and we are proud of it.

We value the expertise of nutrition support dietitians at Coram Healthcare. Nutrition support dietitians are integrated within our organization—in clinical patient care, operations, and sales. Some of you may have heard or read that Coram Healthcare Corporation filed voluntary petitions for relief and a plan of reorganization under Chapter 11 of the U.S. Bankruptcy Code on August 8, 2000. We want you to know why we did this and be assured that this will not affect your patients in any way.

Coram Healthcare was created from the merger of several home infusion companies and has been dealing with high levels of debt for years. The filing simply provides a legal framework for the parent companies to restructure debt, which the lenders have agreed to forgive. This will allow Coram Healthcare to be financially strong and even better positioned to continue as the quality leader in comprehensive home nutrition services.

It is important to note that this has not and will not disrupt supplies, services, or the quality of care provided by the professional staff at our branches. Please understand our Coram branches can and will continue to meet all financial and service obligations to patients, customers, employees and suppliers.

Our commitment to our consumers and you the clinicians, who work with these patients, continues. If you have any questions, please do not hesitate to call me at 1-800-CORAM HC. We value our relationship with you and look forward to providing friendly, caring, and quality service for years to come.

Sincerely,
Carol Ireton-Jones, PhD, RD, LD, CNSD
Director of Nutriti n Services

EXHIBIT D

ADA '99

TITLE:
ENTERAL NUTRITION IN CHRONIC PANCREATITIS: COST SAVINGS WITH THE USE OF A 1.5 KCAL/ML PEPTIDE-BASED DIET

AUTHOR(S):
J. Meyer, RD, LD, CNSD; J.C. Smith, MD, FACP; Health Partners, Bloomington, MN.

LEARNING OUTCOME:
To recognize a cost-effective alternative enteral therapy for use in pancreatitis.

ABSTRACT TEXT:
Parenteral nutrition is routinely employed in patients with pancreatitis. A 42 year old male with chronic pancreatitis, chronic obstructive pulmonary disease, irritable bowel, and a history of alcohol abuse was maintained on home total parenteral nutrition (TPN) for 14 weeks. Despite increasing energy intake from 30 to 44 kcal/kg, he was unable to maintain weight, losing 8 lbs over 9 wks (to 68% of IBW) on 2042 kcal/day.

The decision to trial a 1.0 kcal/mL whey-based peptide diet with 70% of the lipid as medium-chain triglycerides was made. The jejunal feeding was advanced from 10 to 100 mL/hour over a period of two weeks as the TPN was decreased. The diet was then changed to the nutritionally equivalent 1.5 kcal/mL formula at 67 mL/hour and advanced to 150 mL/hour over 10 hours (nocturnal feeding) to provide 2250 kcal/day. The formula change and increased energy intakes were well tolerated. Liver enzymes returned to normal within four weeks of enteral therapy. The patient's energy level improved and he gained weight. Pain and nausea continued to prevent oral intake.

Implementation of this enteral formula in place of TPN resulted in significant cost savings ($625 per wk, $2,500 per mo, or $30,000 per yr). There were clear quality of life benefits for the patient. He was able to receive his caloric requirements as a nocturnal feeding in a reasonable volume and time period, which allowed him to pursue normal activity during the day.

A growing body of research evidence supports the use of whey based peptides in patients with chronic or mild acute pancreatitis. Implementation of this high calorie peptide-based elemental diet resulted in improved clinical outcomes, improved quality of life, and significant cost savings.

EXHIBIT E

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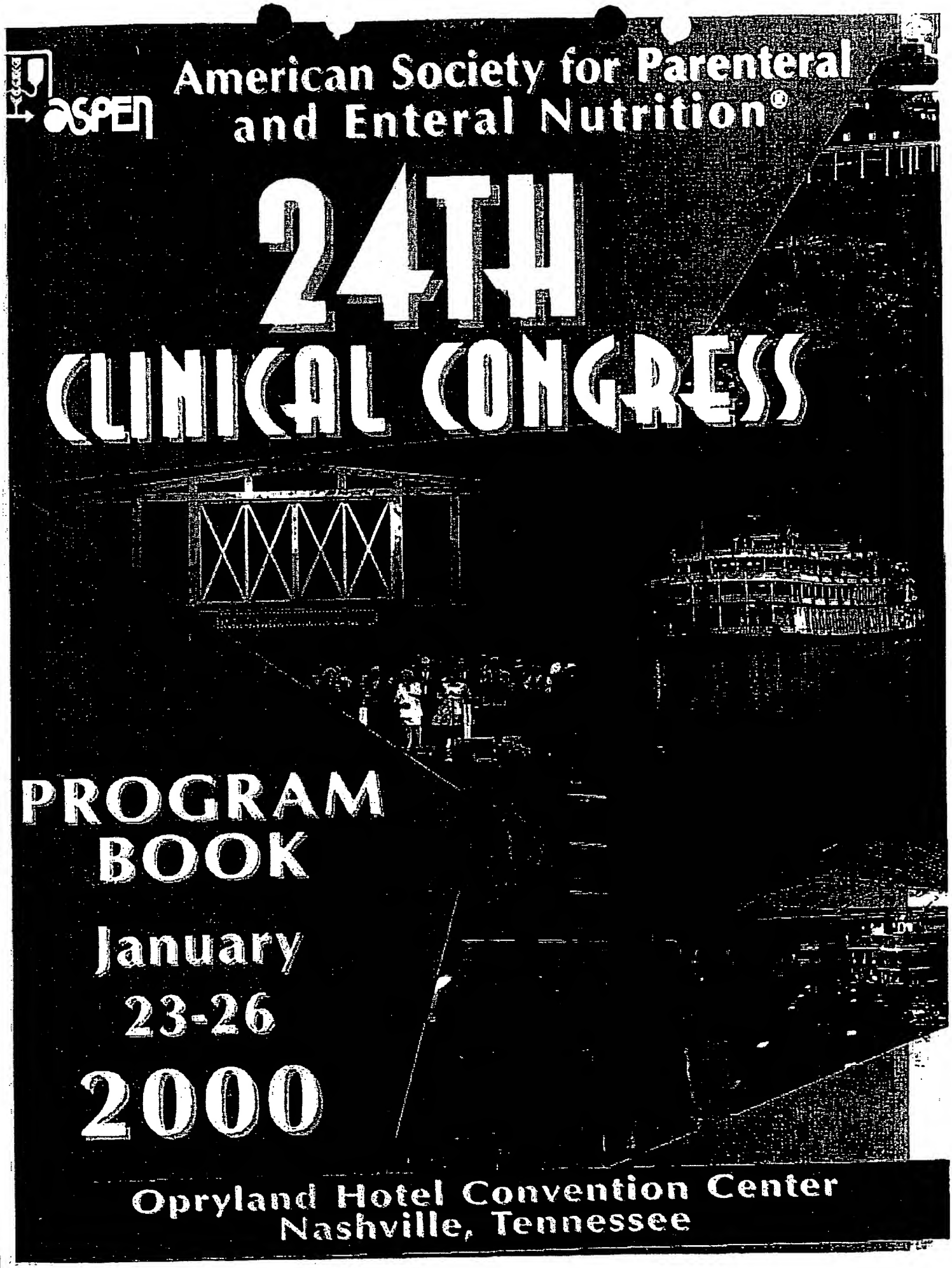
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P0086

Ireton-Jonés Equation vs Indirect Calorimetry In the Estimation of Energy Expenditure of Surgical Patients. Amado De Jesus Athie, Hospital General Dr. Manuel Gea Gonzalez, Torlello Guerra, Mexico, DF

To compare Ireton-Jones equation with indirect calorimetry in the estimation of rest energy expenditure (REE) in surgical patients. Prospective and comparative clinical study. For statistical validation we used ANOVA test and linear correlation coefficient. $p<0.05$. We estimated Rest Energy Expenditure (REE) by the Ireton-Jones equation with parameters for normal breathing patients and by indirect calorimetry in hospitalized patients, from november 1996 thru march 1998. We studied age, weight, height, Body mass index (BMI), overweight percentage, respiratory coefficient (RQ) and non-proteic respiratory coefficient (NPRQ). We divided our patients in 5 groups: group I severe acute pancreatitis, group II enterocutaneous fistulae, group III cancer, group IVsepsis and group V major surgery. Indirect calorimetry was our "Gold Standard" We performed a total of 166 estimations by indirect calorimetry and by the Ireton-Jones equation. The age of our patients was 39.87 + - 14.41 years (M + - SD). We performed40% of our calculations in group I, 31% in group II, 7% in group III, 14% in group IV and 7% in group V. The REE was in 1505 + 400 Kcal/day estimated by calorimetry. The QR was 0.89 + 0.14, and NPQR 0.94 + 0.16. Ireton-Jones equation gave us a REE of 1526 + 247 Kcal/day. These results were for all groups. We got a linear correlation coefficient of 0.5 ($p = 0.0000$) for all groups. The correlation for group I was 0.5 ($p = 0.0000$); for group II 0.5 ($p = 0.0019$), for group III 0.9 ($p = 0.6539$), for group IV 0.7 ($p = 0.3743$) and for group V 0.7 ($p = 0.3534$). The percentage of variation of the equation was 2.46-22.3% for all groups. There is good correlation between Ireton-Jones equation and indirect calorimetry for estimating REE in general population. But with different groups of patients the equation correlates poorly with indirect calorimetry. The error of the equation ranks between 2 to 22%. Indirect Calorimetry continues to be the "Gold Standard" for estimating REE.

P0087

Use of Condensed Semi-elemental Diet in the Treatment of Pediatric Crohn's Disease L. Bouthillier, A. Deslongchamps, B. Seidman, Ste-Justine Hospital, Montreal, Quebec

Nutritional therapy is an effective therapeutic option for pediatric Crohn's disease (CD). In addition to the generally unpopular taste, the large volume of standard defined formula diets (lkcal/ml) that must be consumed during a one-month treatment period (2200-3000 ml per day) can hinder compliance. A retrospective analysis was performed to evaluate the effect of the use of condensed semi-elemental diet (1.5 kcal/ml) (CSED) on the acceptability, route of administration, tolerance, weight gain, and efficacy of nutritional therapy for pediatric CD patients. The medical records of all our CD patients, treated with CSED since October 1998 for either induction of remission (new onset or relapse) (R) or growth failure and relapse prevention (P), were reviewed. Effective treatment was defined as a patient who successfully completed > 4 weeks of strict CSED (50-80 kcal/kg ideal weight/day) and whose disease activity was controlled (Harvey-Bradshaw Index < 4). The use of CSED was noted to be as effective and as well tolerated as other nutritional treatments in pediatric CD. Patients who had previously been treated with standard 1.0 kcal/ml semi-elemental formula (SF) preferred the reduced volume of condensed product required to meet their nutritional needs. More patients on the CSED chose tube feedings over exclusive oral feedings compared with patients in our previous study using SF (60% TF or both for CSED, vs 41% for SF). Average weight gain (% wt change/4 wk treatment) was not significantly different in R or P groups (7.17±4.16 vs 8.14±4.57). There was also no difference in weight gain in regard to route of administration. Overall, our data suggest that the use of CSED improved adherence to therapy and ultimately clinical outcomes.

Table I.

Condition	n	Treatment Effective	Tube Feeding (TF)	Both (>75% TF)	P.O.	% Wt Ga
Remission						
New-Onset	7	4/7	9/18	2/18	7/18	7.17 ± 4.
Relapse	11	7/11				
Growth Failure and Relapse Prevention	7	7/7	3/7	1/7	3/7	8.14 ± 4.
Total	25	18/25	12/25 48%	3/25 12%	10/25 40%	

P0088

Monitoring of Micronutrient Status for a Patient with Short Bowel Syndrome Receiving Home Parenteral Nutrition Results in Improved Outcomes. L. B. Beerman, Comin Healthcare, Omaha, NE

Patients with short bowel syndrome (SBS) may require prolonged use of home parenteral nutrition (HPN) and with careful clinical management HPN needs may be reduced. Routine nutritional assessments help to identify nutrition deficiencies in these patients. A thirty-five year old male with SBS receiving HPN for nine years manifested clinical signs and symptoms of vitamin deficiencies which included dry flaking skin, dull, dry and sparse hair, and splinter hemorrhages on the nails identified on routine six month follow-up. Initial laboratory studies indicated zinc and vitamin C deficiencies. Further investigation revealed multiple vitamin and mineral deficiencies including Vitamins A, D and E, magnesium and copper. Serum manganese level was also elevated. At this time, liver function tests were elevated and the patient desired to decrease infusion time. The HPN was weaned one day each week. In order to meet micronutrient needs, multiple liquid vitamin and mineral preparations were provided as no one preparation met 100% of estimated needs. Over 15 mo with careful nutrient supplementation the patient perceived an improvement in physical signs and symptoms and demonstrated progress in laboratory values. The patient continues to infuse only one day each week making weight maintenance and continued repletion a challenge. Liver function tests remain elevated for unknown reason. On-going monitoring of oral and parenteral vitamin therapy will continue in order to achieve normal serum levels.

P0089

Outcome of Chronic Cholestasis in Adult Patients Receiving Home Parenteral Nutrition. C. Chambrier, M. Bonnomprix, Gerard, S. Bryssine, D. Robert, Centre Agree de Nutrition Parenterale a domicile, Lyon; P. Boulezreau, Hopital Edouard Herriot, Lyon

Chronic cholestasis (defined as 2 out of 3 abnormalities for at least 6 months: total bilirubin, alkaline phosphatases or -GT > N) is a major complication of long-term parenteral nutrition (after the fifth year) but little information is known about its evolution

EXHIBIT F

European Journal of Clinical Nutrition (2002) 56, 1–3,
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ORIGINAL COMMUNICATION

Gastric emptying of two whey-based formulas of different energy density and its clinical implication in children with volume intolerance

V Khoshoo[1] and S Brown[1]

[1]*West Jefferson Medical Center, New Orleans, Louisiana, USA*

Objective: Whey-based formulas have faster gastric emptying than casein-based formulas. Isocaloric, isovolumic, whey-based formulas of different osmolarity and fat content empty in a similar manner. Will the gastric emptying of high and low energy density whey-based formulas be similar?
Design: We studied the gastric emptying rate of equal volumes of two whey-based formulas of different energy density (4.18 kJ/ml and 6.27 kJ/ml) and osmolality (270 and 450 mOsm/kg, respectively) in 10 children (4.5–12y) with volume intolerance and resultant inability to gain weight.
Results: The two formulas had comparable gastric emptying rates at 30, 60, 90 and 120 min. Over a one month clinical trial, substitution of the lower energy density whey-based formula (no weight gain over 2 months) with an equal volume of the high energy density formula produced a mean weight gain of 1.17 ± 0.5 kg per patient without change in tolerance.
Conclusion: The higher density whey-based formula can safely substitute an equal volume of a lower energy density formula to produce weight gain without affecting tolerance.
Implication: This provides an important intervention for increasing energy intake in children with volume intolerance or fluid restriction. 56(7):656-658.
European Journal of Clinical Nutrition (2002) 56, 000–000. DOI: 10.1038/sj/ejcn/1601373

Keywords: gastric emptying; whey; feeding intolerance

Introduction

Gastric emptying of liquids is influenced by several factors, particularly type and content of fat, volume and osmolarity. The most important factor, which governs gastric emptying, is the energy content of the meal and it overrides the energy composition of the meal (Hunt *et al*, 1985; Hunt & Stubbs, 1975). Earlier, we have shown that the type of protein is also an important factor that affects gastric emptying of liquid formulas (Fried *et al*, 1992). Different types of isoenergetic, isovolumic whey-based formulas empty faster than similar casein-based formulas and are associated with fewer episodes of emesis and gastroesophageal reflux (Fried *et al*, 1992; Khoshoo *et al*, 1996; Billeaud *et al*, 1990; Tolia *et al*, 1992). This effect is seen irrespective of the osmolarity, fat composition or nature of whey. The next logical step is to evaluate whether the presence of whey as the protein moiety will override the energy content of the meal in influencing gastric emptying of a liquid formula. We studied the gastric emptying rates of equal volumes of two similar whey-based formulas of different energy densities, ie 4.18 and 6.27 kJ/ml, in children with volume intolerance and also assessed weight gain.

Methods

This study was conducted in a prospective manner after approval from the Institutional Review Board. The study population comprised of 10 children with spastic quadri-

*Correspondence: V Khoshoo, 4709 Butternut Place, Midland, MI 48640, USA.
E-mail: vkhoshoo@earthlink.net
① *Guarantor:* ■
Contributors: ■
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plegia (4.5–12 y; six male, four female) who were fed exclusively through a gastrostomy tube using bolus feeds. All children were referred to the Pediatric Gastroenterology and Nutriti n Clinic more than 6 months prior to the study for poor weight gain secondary to volume intolerance as manifested by gagging, discomfort or emesis following bolus feeds. To hasten gastric emptying and improve tolerance the formula had already been switched to a whey-based formula; however, the children were still unable to advance the volume to optimize energy intake for weight gain. For this reason all patients had failed to gain any weight during the previous 2 months. They were all managed by the same physician, on an intent-to-treat basis. After obtaining written consent and overnight fast a Tc99 sulfur colloid gastric emptying scan was performed with 150 ml of either of the two formulas in random allocation as described before (Fried *et al*, 1992). After at least 48 h, to allow time for decay of radioactivity, a similar scan was repeated with the other formula. All conditions were kept identical during both scans including timing of the scans. Each scan was performed for 120 min. The radiologist performing and interpreting the scans was unaware of the formula used. The formulas used were: Peptamen (4.18 kJ/ml, 270 mOsmol/kg) and Peptamen 1.5 (6.27 kJ/ml, 450 mOsmol/kg). These formulas were selected because despite different energy densities they have a similar energy composition and both formulas are commercially available (Nestle Clinical Nutrition Inc., Deerfield, IL, USA), hence have immediate patient care relevance. The composition of these formulas is provided in Table 1. Following the second scan the formula was switched to Peptamen 1.5 but delivered in the exact same manner as Peptamen, ie same volume, duration of infusion and feeding schedule. The parents were asked to maintain a diary of symptoms suggesting intolerance, ie gagging, discomfort, emesis and diarrhea. A 1 month trial of this higher energy formula was given during which time nude body weights were monitored on a weekly basis. Following this period the nutritional intervention was reassessed and appropriate changes were made with a view to optimizing nutritional status. Data on individual patients and groups was compared using a paired *t*-test and two-way ANOVA for repeated measures.

Table 1 Energy composition of the two whey-based formulas per 1000 ml

	Peptamen	Peptamen 1.5
Energy (kJ)	418	627
Protein (g)	40 (16)	60 (16)
Carbohydrate (g)	127 (51)[a]	191 (51)[b]
Fat (g)	39 (33)	58.5 (33)

Figures in parentheses denote percentage contribution to total energy. The fat blend in both formulas comprises medium and long chain triglycerides in the ratio of 70:30, respectively
[a]Maltodextrins 88%; corn starch 12%. [b]Maltodextrins 91%; corn starch 9%.

Results

All patients were clinically stable with normal hydrati n status (urin specific gravity < 1.025), normal thyroid functions (thyroxine, thyroid stimulating hormone), serum albumin and electrolytes (Na, K, Cl, Mg, Ca and CO_2). Each patient served as his/her own control. The gastric emptying of the two formulas, at all phases of the 120 min study period was similar in all patients individually ($P > 0.05$). The mean ± s.d. percentage residual gastric activity of the two formulas at 30, 60, 90 and 120 min was similar ($P > 0.05$) and is given in Table 2. Eight of these 10 patients were enrolled for the clinical trial with Peptamen 1.5. Two patients were excluded because they were considered unreliable. Patients were considered unreliable if they had a history of having missed more than two clinic appointments over the past 1 y without sufficient reason. This was important to predetermine because we felt that the semi-objective data on tolerance recorded by the parents over the course of the 1 month trial with Peptamen 1.5 needed to be recorded conscientiously and in an extremely reliable manner. The mean weight gain over the 1 month trial period with equal volume of Peptamen 1.5 (1.17 ± 0.5 kg) was significantly greater than ($P < 0.05$) the no weight gain observed over the previous 2 months while consuming Peptamen. The parents reported no change in general symptoms, symptoms of tolerance or stooling pattern during the trial with Peptamen 1.5 as compared to while the children were consuming an equal volume and identical feeding schedule with Peptamen.

Discussion

Gastric emptying of liquid formulas is affected by several factors. Increased osmolarity and a higher fat content delay gastric emptying. The energy content of a meal, irrespective of its composition, has been shown to be the most important factor that affects the gastric emptying of a meal (Hunt *et al*, 1985; Hunt & Stubbs, 1975). We have shown that the nature of protein is another factor that influences the gastric emptying of a liquid meal, irrespective of osmolarity and energy composition, ie whey-based formulas empty the stomach faster than equal volumes of isoenergetic casein-based formulas (Fried *et al*, 1992). However, equal volumes and energy content of different whey-based formulas empty the stomach in a comparable manner despite differences in their composition, ie a hyperosmolar, intact whey-based formula;

Table 2 Mean (s.d.) percentage residual gastric activity at different time intervals with 150 ml of the two formulas

	30 min	60 min	90 min	120 min
Peptamen	74 (11)	57 (9.4)	43 (13)	27.5 (16.3)
Peptamen 1.5	77 (11.5)	60 (12.4)	47 (16.3)	31.4 (19.9)

$P > 0.05$ for all comparisons between the two formulas at different time intervals.

a hyperosmolar, whey hydrolysate-based formula and an isoosmolar, whey hydrolysate-based formula with fat content predominantly as medium chain triglycerides (Fried *et al*, 1992). This clearly implies that the nature of protein, ie whey, overrides the osmolarity and fat content of a formula in affecting its gastric emptying. Therefore whey as well as the energy content of the meal emerge as the two most important determinants of gastric emptying. Data from the present study suggests that the presence of whey as the protein moiety in a liquid formula will override the effects of the energy content of the meal since equal volumes of two similar whey-based formulas of very different energy densities were shown to empty at similar rates despite a major difference in osmolarity and total fat, carbohydrate and protein content. These findings were corroborated during a one-month trial of Peptamen 1.5, the whey-based formula with higher energy density. In accordance with the results of the gastric emptying scans, and as expected, there was no change in tolerance after the formula was changed from Peptamen to an equal volume of Peptamen 1.5 and produced the desired outcome of a significant weight gain.

In conclusion, our present study shows that higher density whey-based formulas could be effectively delivered to produce weight gain without change in tolerance in children receiving lower density whey-based formula and who have reached their maximum tolerated volume and fail to gain further weight. We already know that whey-based formulas empty faster than casein-based formulas. It is then logical to state that a higher density whey-based formula can safely substitute equal volume of lower energy density whey or casein-based formula. This provides the basis of an effective intervention to increase energy intake in patients with volume intolerance or fluid restriction without compromising tolerance.

Acknowledgements

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References

Billeaud C, Guillet J & Sandler B (1990): Gastric emptying in infants with or without gastroesophageal reflux according to the type of milk. *Eur. J. Clin. Nutr.* 44, 577–583.

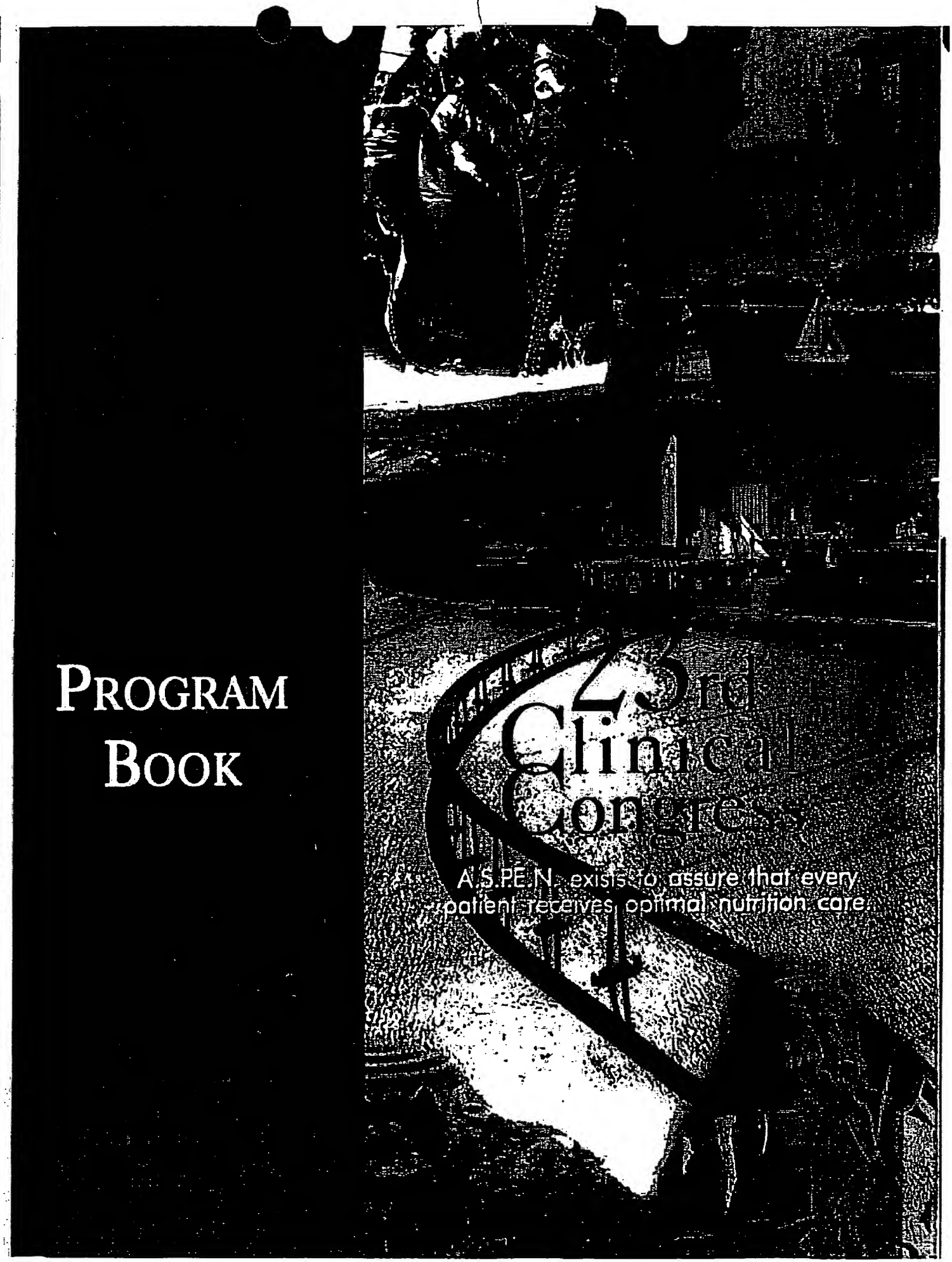
Fried MD, Khoshoo V, Secker DJ, Gilday DL, Ash JM & Pencharz PB (1992): Decrease in gastric emptying time and episodes of regurgitation in children with spastic quadriplegia fed a whey-based formula. *J. Pediatr.* 120, 569–572.

Hunt JN & Stubbs DF (1975): The volume and energy content of meals as determinants of gastric emptying. *J. Physiol.* 245, 209–225.

Hunt JN, Smith JL & Jiang CL (1985): Effect of meal volume and energy density on the gastric emptying of carbohydrates. *Gastroenterology* 89, 1326–1330.

Khoshoo V, Zembo M, King A *et al* (1996): Incidence of gastroesophageal reflux with whey- and casein-based formulas in infants and in children with severe neurological impairment. *J. Pediatr. Gastroenterol. Nutr.* 22, 48–55.

Tolia V, Lin CH & Kuhns LR (1992): Gastric emptying using three different formulas in infants with gastroesophageal reflux. *J. Pediatr. Gastroenterol. Nutr.* 15, 297–301.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patient receives optimal nutrition care.

[illegible] Formula for Gastrostomy Tube Feedings
[illegible], RD and D.M. Orenstein, MD; [illegible] Hospital of Pittsburgh, Pittsburgh PA.

[illegible] recessively inherited chronic [illegible]. Caloric needs of children with CF are elevated [illegible] of breathing, an elevated metabolic rate, and [illegible] of fat malabsorption from pancreatic [illegible] with CF has been positively correlated with [illegible] can promote normal growth, improve [illegible] quality of life. [illegible] normal growth with a high caloric [illegible] tube feedings) has been shown to be beneficial. [illegible] feeding at our CF center involves allowing the child [illegible] day and then receive continuous gastrostomy tube [illegible] predominantly used at our center is a low fat, semi- [illegible] to a caloric density of 1.5 calories/mL. [illegible] of this formula in the CF population are threefold: 1) a high [illegible] content (74% of total kcal) which can aggravate hyperglycemia, 2) [illegible] prepared with a blender or mixer which is inconvenient and increases the [illegible] formula contamination, and 3) high cost. This formula has been [illegible] CF patients because of its low fat content and subsequent reduced need for pancreatic enzymes.

To investigate the utility of a lower carbohydrate semi-elemental tube feeding, four children with CF and pancreatic insufficiency were administered a 1.5 kcal/mL formula with 31% of total kcal as carbohydrate for gastrostomy tube feedings. Oral pancreatic enzymes were given at the beginning and end of each nightly feeding. All four children experienced improvements in weight gain and no steatorrhea was reported. Advantages of the ready-to-feed, semi-elemental diet for the CF population include a carbohydrate content of 31% of total calories, a caloric density of 1.5 kcal/mL, a low osmolality (450 mOsm/kg, unflavored) to minimize diarrhea, a medium chain : long chain triglyceride ratio of 70:30 to aid absorption and decrease pancreatic enzyme requirements, a convenient ready-to-use form and decreased cost.

Life expectancy continues to increase for people with CF and enteral feedings have been shown to play a significant role in improving nutrition status. These data demonstrate advantages to using a 1.5 kcal/mL, semi-elemental, ready-to-feed formula in CF patients on gastrostomy tube feedings.

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Long Term Surgical Jejunostomy Feeding in Young Children with Gastroesophageal Reflux and Asthma.

B.Björnestam, RN; C.Bergström, RD; S.Bergdahl, MD; Y.Finkel, MD. Astrid Lindgren's Children's Hospital, Karolinska Hospital, Stockholm, Sweden

Gastroesophageal reflux disease (GERD) is common in children with neurological disease and in children with congenital esophageal anomalies. GERD in young children is associated with with feeding difficulties and may also contribute to wheezing and asthma. The vicious cycle of GERD-feeding problems-asthma-GERD is difficult to break. Nissen fundoplication (NF) is effective, however significant long-term postoperative morbidity is common.In this study children with GERD and asthma fulfilling the criteria for fundoplication but medically unfit for NF had a surgical jejunostomy feeding (JF) tube placed. Aim: To evaluate long-term JF. Subjects and Methods: Six children, 4 boys, with severe GERD, feeding difficulties and chronic asthma were included in the study. 3 children, 2 boys, had profound neurological impairment, 1 post-op gastroesophageal atresia, 1 post-op diaphragmatic hernia and 1 VLBW with BPD. Jejunostomy feeding tube was placed at median age 14.5 months (3 -18) and continuous pump-feeding 16-18 hours daily at home was started. The outcome of the treatment was evaluated by measuring the frequency of respiratory problems, vomiting, acute hospital admissions, antropometry and by questionnaire filled in by all the parents. Results: Median time for JF was 6 months (5-12), total 44 months. Vomiting and acute hospital admissions were considerably reduced in all children. 4/6 children had catch-up in growth during JF. Respiratory problems and use of inhalation medication were reduced in 3/6, unchanged in 2/6, worsened in 1. Postoperative wound complications was seen in one child and healed promptly. The jejunostomy tubes fell out more than once in all children, and were replaced by the parents at home. All parents expressed satisfaction with the outcome of the treatment for their child. Conclusion: Long-term JF is feasible in young children with GERD and asthma.

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Abstract Withdrawn

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Case Study: Successful Use of B Vitamins to Reduce Homocysteine Levels in a Parenterally-fed Patient with a History of Mesenteric Ischemia

K. Willcutts, RD; H. Blackwood, RN; T. Sims, RD; [illegible], MD, University of Virginia Hospital, Charlottesville, VA

Recent research has shown that hyperhomocysteinemia is a significant, [illegible] risk factor for arterial and venous thrombosis. The mechanism for this is not completely understood. However, it is known that high intakes of folic acid can [illegible] homocysteine levels and that folic acid is only effective if the patient is not [illegible] in vitamin B-12. Vitamin B-6 has been shown to [illegible] levels. Therefore, many cardiologists recommend supplementation of folic acid, vitamins B-12 and B-6 for their patients. To our knowledge, no research has been published that addresses the use of these vitamins to lower homocysteine levels in patients with a history of mesenteric ischemia of otherwise [illegible]. A 65 yo female was admitted on 3/24/98 with nausea, vomiting, and abdominal distension after multiple admissions for bowel obstruction. A mesenteric arteriogram revealed embolic occlusion of several mesenteric vessels as well as the left renal artery. Tests done to identify an embolic source were negative. Then a hypercoagulable work-up was performed. The work-up [illegible] hyperhomocysteinemia. Supplemental folic acid 2 mg/d, vitamin B-12 1 mg/d [illegible] vitamin B-6 200mg/d were started and have been continued since then. The patient was discharged home on total parenteral nutrition (TPN) (which included the supplemental B vitamins) and coumadin for a waiting period to allow for healing of her abdomen, to replenish her malnourished state, and to allow time for increased collateral vessel development. She did well at home except for failed several attempts to start enteral nutrition. A repeat mesenteric arteriogram on [illegible] revealed increased collateral development of mesenteric vessels. On 6/20 a laparotomy was performed at which time a 20 cm segment of chronically ischemic strictured small bowel was resected and reanastomosed. The pathology report confirmed the diagnosis of chronic ischemia. The rest of the gut was healthy. The patient was discharged home tolerating a regular diet and off TPN. The result of a follow-up laboratory test on 7/2 was a low normal homocysteine level. Therefore, she was instructed to continue her supplemental vitamins to prevent elevation in her homocysteine level. She also continues to take coumadin. She has been tolerating a regular diet at home since then. This case study illustrates the need for more research to determine the prevalence of hyperhomocysteinemia in patients with chronic mesenteric ischemia and to measure the effectiveness of supplemental B vitamins in managing these patients.

EXHIBIT G